Prevalence of Anti-Gelatin IgE Antibodies in People With Anaphylaxis After Measles-Mumps-Rubella Vaccine in the United States

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ABSTRACT. *Objective.* **Anaphylaxis after immunization, although rare, is serious and potentially life-threatening. Understanding risk factors for this reaction is therefore important. Gelatin is added to many vaccines as a heat stabilizer. Japanese researchers have demonstrated a strong association between immediate hypersensitivity reactions to measles, mumps, rubella, varicella, and Japanese encephalitis immunizations and subsequent detection of anti-gelatin immunoglobulin E (IgE) antibodies. They suggested that previous receipt by these patients of diphtheria-tetanus-acellular pertussis vaccines with trace amounts of gelatin was responsible for the sensitization. We aimed to assess whether a similar association exists for vaccinees in the United States who reported anaphylaxis after receipt of measles-mumps-rubella (MMR) or measles vaccines and to review recent trends in reporting of hypersensitivity reactions.**

Methods. **We conducted a retrospective case-control study. Cases of anaphylaxis that met a predefined case definition were identified from the US Vaccine Adverse Event Reporting System (VAERS). Mayo Clinic patients who received MMR vaccine uneventfully served as controls. The study subjects were interviewed to obtain the history of allergies. Sera from study subjects and their matched controls were tested for IgE antibodies to gelatin, whole egg, and vaccine viral antigens using solid-phase radioimmunoassay. Data from the Biologics Surveillance System on annual numbers of doses of MMR and varicella vaccines distributed in the United States were used to evaluate possible changes in reporting of selected allergic adverse events.**

Results. **Fifty-seven study subjects were recruited into the study and interviewed. Of these, 22 provided serum samples for IgE testing. Twenty-seven subjects served as a comparison group and provided a sample for IgE testing; 21 of these completed an allergy history questionnaire. Self-reported history of food allergies was present more frequently in the interviewed study subjects than in the controls, whereas the proportions of people with other characteristics were similar in both groups. None of the interviewed people had a history of food allergy to gelatin. The level of anti-gelatin IgE antibodies was significantly higher among study subjects than among controls, whereas the levels of IgE antibodies against egg and all 3 viral antigens did not differ significantly. Of 22 study subjects, 6 (27%) tested positive for anti-gelatin IgE, whereas none of the 27 controls did. The rate of anaphylactic reactions reported to VAERS after measles virus–containing immunization in the United States between 1991 and 1997 is 1.8 per 1 million doses distributed. No substantial increase in the number of reported allergic events after frequently used gelatin containing MMR and varicella vaccines could be observed during the first 4 years (1997–2000) since the introduction of diphtheria-tetanus-acellular pertussis vaccines for use in infancy.**

Conclusion. **Anaphylactic reactions to MMR in the United States are rare. The reporting rate has the same order of magnitude as estimates from other countries. Almost one fourth of patients with reported anaphylaxis after MMR seem to have hypersensitivity to gelatin in the vaccine. They may be at higher risk of developing anaphylaxis to subsequent doses of other gelatin-containing vaccines. These people should seek an allergy evaluation before such immunization.** *Pediatrics* **2002; 110(6). URL: http://www.pediatrics.org/cgi/content/full/110/6/e71; *anaphylaxis, gelatin, measles-mumps-rubella vaccine, VAERS, vaccine adverse reactions.***

ABBREVIATIONS. MMR, measles-mumps-rubella; IgE, immunoglobulin E; DTaP, diphtheria-tetanus-acellular pertussis; CDC, Centers for Disease Control and Prevention; VAERS, Vaccine Adverse Event Reporting System; COSTART, *Coding Symbols for Thesaurus of Adverse Reaction Terms*; CPM, counts per minute; OPV, oral polio vaccine; HiB, *Haemophilus influenzae* type B.

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Received for publication Feb 11, 2002; accepted Aug 12, 2002.

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Anaphylactic shock as a result of immunization is extremely rare but very serious and potentially life-threatening.[1] Efforts to better understand and prevent it are therefore warranted. In a review of adverse events associated with childhood vaccines, the Institute of Medicine concluded in 1994 that the evidence establishes a causal relationship between measles-mumps-rubella (MMR) vaccination and anaphylaxis; estimates of the risk ranged from 1/20 000 to 1/1 000 000 doses distributed.[1] No responsible allergen(s) could be identified at that time. Immediate reactions to MMR have been attributed to egg allergy because MMR may contain small amounts of egg proteins from the process of cultur-

ing the measles and mumps viruses.[2] (M-M-R II product circular 9265201, February 2000). However, multiple examples of uneventful administration of this vaccine to hundreds of children with known hypersensitivity to egg, as well as reports of anaphylaxis to MMR in people without the history of allergy to eggs, cast doubt that egg proteins in the vaccine are major causative agents.[3–5] Any of the other MMR components and excipients—viral antigens, neomycin, sorbitol, gelatin, and latex from vaccine vial rubber stoppers—could potentially be responsible for an immunoglobulin E (IgE)-mediated reaction.

In 1993, Kelso et al[6] first documented a case in which an anaphylactic reaction after MMR II was traced to the gelatin component of the vaccine (14.5 mg of gelatin per dose, according to the manufacturer). After this US report, several Japanese researchers found a similar association in an unusually high proportion of patients. Sakaguchi et al[7,8] found that 24 of 26 children with systemic immediate reactions to measles vaccination had anti-gelatin IgE antibodies; of these, 7 had allergic signs and symptoms on ingestion of gelatin-containing foods (2 had reactions before vaccination, and 5 had reactions after vaccination). All of the control children without allergic reactions to the vaccines lacked anti-gelatin IgE. Subsequent studies from Japan suggested that immediate and delayed allergic reactions after other gelatin-containing vaccines (against varicella and Japanese encephalitis) may have been associated with prevaccine sensitization to gelatin.[9,10] Nakayama et al[11] suggested that usage of gelatin-containing diphtheria-tetanus-acellular pertussis (DTaP) vaccines before immunization with live virus vaccines may have served as a possible source of such a sensitization. Only 1 other publication from the United States reported a link between an immediate hypersensitivity reaction (severe urticaria) to a gelatin-containing vaccine (Varivax) and presence of hypersensitivity to gelatin demonstrated by a positive intradermal test with porcine gelatin in the same concentration as in the vaccine.[12] Neither of the 2 patients described had food allergy to gelatin before varicella immunization.

Objectives of this study were to examine whether people with anaphylaxis after receipt of measles virus–containing vaccines in the United States have an unusual profile of self-reported allergies and whether they have significantly higher levels of anti-gelatin IgE antibodies compared with healthy controls. We were also interested in reviewing trends in reporting of selected hypersensitivity adverse events reported after MMR and varicella immunization for the periods before and after introduction of gelatin-containing DTaP vaccines in the US vaccination schedule.

METHODS

We conducted a retrospective case-control study comparing self-reported allergy histories and IgE antibody levels in people with and without reported symptoms of immediate hypersensitivity after MMR vaccination. The study protocol was approved by institutional review boards at the Centers for Disease Control and Prevention (CDC) and Mayo Clinic. Written and signed consent forms were provided by all study subjects. Study subjects were selected from the database of the Vaccine Adverse Event Reporting System (VAERS). VAERS is the national surveillance system operated by the CDC and the US Food and Drug Administration. Detailed descriptions of the system and its uses and limitations appear elsewhere.[13–15] VAERS collects information on vaccine adverse events from vaccine providers, vaccine manufacturers, and vaccinees or their parents. The reported symptoms, diagnoses, and laboratory findings are categorized using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART).[16] We searched the VAERS database for reports that met the following 3 criteria: 1) included COSTART codes for anaphylaxis, allergic reaction, or specific dermatologic symptom(s) with respiratory and/or gastrointestinal symptom(s); 2) had onset of symptoms on the day of vaccination; and 3) followed measles virus–containing vaccine administered alone or in combination with other vaccines, except the ones that contained significant amounts of gelatin (varicella vaccine, yellow fever, Japanese encephalitis, rabies, and influenza vaccines). The reports were then manually reviewed and classified by one of us (J.M.K.) using the following working definitions:

1. Probable case: The report describes evidence of a mast cell–mediated reaction occurring within 4 hours of vaccine administration including at lease 1 dermatologic sign or symptom (pruritus, urticaria, angioedema, flushing) and 1 or more signs and symptoms from any of the following systems: respiratory (dyspnea, bronchospasm, glossal or pharyngeal edema, hoarseness, nose/eye symptoms, nasal congestion, rhinorrhea, sneezing, red itchy watery eyes), cardiovascular (hypotension, lightheadedness, loss of consciousness, syncope, tachycardia, palpitation), or gastrointestinal (nausea, vomiting, diarrhea, bloating, abdominal pain).
2. Possible case: The report describes dermatologic or respiratory symptoms (but not both) within 4 hours of immunization. Alternatively, the reaction includes 1 or both dermatologic and respiratory symptom(s) but happened >4 hours after vaccination.
3. Noncase: The report describes an adverse reaction occurring within 24 hours of vaccine administration not defined as 1 or 2 above.
4. Reports with insufficient information: The report was coded as anaphylaxis without sufficient description of the event for categorization above (ie, no description of the onset interval and/or the symptoms).

We attempted to contact by mail all probable and possible cases of anaphylaxis reported to VAERS between 1991 and 1997. Those who agreed to participate in the study were interviewed by telephone about the vaccine adverse event and history of possible allergies to food, environment, and drugs. Those who mentioned any allergy were asked to specify to what they were allergic and the timing of onset and symptoms. For study subjects younger than 17 years, parents or guardians were interviewed. The interviewer was not blinded to the case-control status of the study participants. People who completed the interview were asked to submit a blood sample through their health care providers.

Two sources of controls were available for this study: 1) people who reported nonallergic adverse events to VAERS after MMR vaccination (eg, local or a systemic reactions occurring 1–30 days after immunization) and 2) people from the Mayo clinic primary care population, as well as Mayo clinic employees, who received MMR in the past without clinically apparent adverse symptoms. Candidate controls from both groups were matched to study subjects on gender, year of vaccination, and age at vaccination (for study subjects who were younger than 6 years, matched controls were born within 6 months of study subjects; for study subjects who were aged 6–11 years, within 1 year; and for study subjects who were aged 12 and older, within 5 years). Several candidate controls per study subject were available from both sources. For controls from VAERS, the 3 best matched controls from VAERS were contacted, interviewed, and asked to provide a blood sample in the same manner as the study subjects. Mayo clinic controls (or, in case of a minor, their parents), randomly selected from a list of available matches, were contacted via letter and asked to participate in the study and fill in an allergy questionnaire. Those who responded with an affirmative answer were contacted again with instructions to obtain a venipuncture at the clinic. Controls who consented but did not fill in the questionnaire could still provide a blood sample for laboratory testing.

The samples were received and stored at −18°C at a CDC laboratory. Sera from each study subject and its matched controls were tested on the same day, in the same assay. IgE antibodies to gelatin, whole egg, and vaccine viral antigens were measured by solid-phase radioimmunoassay in the Allergic Diseases Research Laboratory at the Mayo Clinic. Methods for preparing and performing the IgE antibody immunoassay appear elsewhere.[6,17] The laboratory workers were blinded to the case-control status of the samples. The results of IgE testing were expressed as the percentage of the total radioactive counts per minute (CPM) that were bound to the solid-phase allergen. Differences in the proportion of people with reported allergies among study subjects and controls were analyzed using χ^2 and Fisher exact tests. The significance of differences in mean CPM values between the study subjects and control groups was determined using paired *t* tests. To account for differences in matching (there were 1–3 controls per study subjects), as well as for inter- and intra-assay variability (sera were tested in 2 batches), we used a more appropriate regression method—the random effect model.[18] To determine the proportion of study subjects with positive IgE test results, we used the following approach. We first calculated the mean CPM value and its standard deviation for the controls. Then the threshold level of the radioimmunoassay test was defined as mean ± 3 standard deviations. Subjects with CPM above this cutoff value were considered to have positive results.

To assess recent trends in reporting of selected hypersensitivity adverse events, we used automated VAERS data. We determined yearly numbers of reports after MMR and varicella vaccines (administered alone or in combination with each other and/or other vaccines) that were submitted between 1991 and 2000 and that had COSTART codes for anaphylaxis, urticaria, and/or wheezing and the onset of symptoms on the day of vaccination. Year-to-year changes in these numbers were compared with trends in annual vaccine distribution based on data from the CDC Biologics Surveillance System (expressed as millions of doses of the corresponding vaccines distributed).

RESULTS

Of the reports submitted to VAERS between 1991 and 1997, 168 were classified as probable or possible cases of anaphylaxis. Of these, 16 (10%) had no contact information on the form. Therefore, 152 cases were contacted by mail. Of these, 95 (63%) could not be recruited because of outdated or incorrect contact information, nonresponse, or refusal. The remaining 57 (37%) people were interviewed and completed the allergy history questionnaire. Of these, 22 (39%) agreed to provide a blood sample for IgE testing; their ages ranged from 15 months to 33 years (mean: 13 years), and 13 (59%) were female. Eleven of these people received MMR vaccine alone, 9 received MMR with 1 or 2 other vaccines (diphtheria-tetanus-pertussis, tetanus-diphtheria, oral polio vaccine (OPV), *Haemophilus influenzae* type B [HiB], or hepatitis B), and 2 received single-antigen measles vaccine only. Five study subjects had received a dose of MMR previously without any allergic symptoms. Among 35 study subjects who did not submit blood samples, there were 21 females and 14 males; their ages ranged from 13 months to 36 years (mean: 6 years). Ten of these people received MMR alone; the remaining 25 received MMR with 1 or more other vaccines (diphtheria-tetanus-pertussis, DTaP, OPV, diphtheria and tetanus, tetanus-diphtheria, HiB, hepatitis B, or varicella vaccine).

Among 57 study subjects who completed the telephone survey, 34 (60%) reported having a history of sensitivity to food, drug, and/or environmental allergens. Of these, food allergies were reported by 16 (pork, beef, eggs, chicken, turkey, dairy products, fish, soy, lentils, peanuts, and chocolate); 16 people remembered hypersensitivity reaction to drugs (penicillin, vancomycin, cephalosporin, amoxicillin-clavulanate potassium combination, codeine, aspirin, ibuprofen, trimethoprim, and sulfamethoxazole); 1 had latex allergy, 1 had allergy to neomycin; 15 were sensitive to environmental allergens (dust mites, mold spores, pollen, grass, cats, dogs, horses, and weeds), and 11 had a history of asthma.

Twenty VAERS controls were recruited and completed the allergy history questionnaire. None of these people reported having allergies to foods; 4 reported hypersensitivity to drugs (cefaclor, amoxicillin-clavulanate potassium combination, codeine, and penicillin), 1 reported hypersensitivity to latex, 3 reported hypersensitivity to environmental allergens (pollen, cats), and 4 had a history of asthma. Only 1 of these VAERS controls submitted a blood sample for IgE testing, however. Because of the difficulties with obtaining sera from these subjects, we decided to use controls from the Mayo Clinic for the laboratory analysis part of the study. Nevertheless, the information received from the interviewed VAERS controls was used in the analysis of allergy histories.

A total of 27 Mayo Clinic controls were recruited and provided a blood sample for IgE testing. As a result, 1 study subject had 3 matched controls and 3 study subjects had 2 matched controls; the remaining 18 study subjects had 1 matched control each. Of the 27 controls, 21 also completed an allergy history questionnaire. None reported having allergy to food; 4 had drug allergies (amoxicillin-clavulanate potassium combination, sulfa), 1 had allergy to latex, and 3 had a history of asthma.

Table 1 compares the reported history of allergies among all interviewed study subjects and controls. Of 57 study subjects, 16 (28%) reported having allergy to foods, whereas none of the controls had reported food allergy. There were no statistically significant differences between study subjects and controls in proportions of people with hypersensitivity to drugs, including neomycin, environmental allergens, and latex. None of the study subjects or

TABLE 1. Comparison of Self-Reported History of Allergies in 57 Interviewed Study Subjects Versus 41 Interviewed Controls

	No. of People With Allergy to					No. of Patients With History of Asthma
	Foods	Drugs	Environmental Allergens	Neomycin	Latex	
Study subjects*	16	16	15	1	1	11
Controls*	0	8	5	0	2	7
P value	<.001†	.5	.6†	.6†	.1†	.9

* Several study subjects and controls had multiple (food, drug, and/or environmental) allergies.
† Obtained using Fisher exact test.

controls interviewed recalled having allergy to gelatin.

Samples received from study subjects and controls were stored in a freezer at the CDC measles laboratory between August 1997 and October 1998 and analyzed in 2 batches (each with sera from 11 study subjects and their corresponding controls). The IgE antibody assays for testing of each batch were run at Mayo Clinic on separate dates. Combined results from both assays are presented in Table 2. The mean CPM value for anti-gelatin IgE antibodies in the group of study subjects ($N = 22$) was significantly higher than in the group of controls ($N = 27$). The P value in paired t test and general linear model was 0.01. The mean CPM values of IgE antibodies against egg and all 3 viral antigens did not differ significantly between study subjects and controls.

Of 22 study subjects, 6 (1, 2, 3, 13, 14, and 22) tested positive for anti-gelatin IgE, whereas none of the controls did (Table 3). Study subject 1 also tested positive for anti-egg IgE. Study subject 10 had elevated anti-measles IgE antibodies. All other study subjects and controls had negative IgE test results. Among the 22 IgE-tested study subjects, the number of people who reported having allergies was 16 versus 19 among the remaining 35 subjects who were not tested. The difference between these proportions was not statistically significant. A brief history of each subject who tested positive for IgE antibody is presented below.

Study subject 1 (positive for anti-egg and anti-gelatin IgE): A 4-year-old white boy received the second dose of MMR on January 23, 1995, and within 10 minutes developed symptoms of facial flushing, hives, cough without wheezing, and hypotension. The boy was treated with diphenhydramine and recovered. He had a history of sensitization to eggs, manifested by a positive skin test; however, he was able to eat foods that contain eggs without problems. He also was allergic (hives) to peanuts, cats, dogs, sesame seeds, ragweed, milk, and house dust (all determined by skin test). He had a history of asthma, well controlled at the moment of immunization. The condition was interpreted by the consulting allergist as a reaction to neomycin. In June 1995, 2 minutes after receiving a dose of Varivax, he developed urticaria for which he was treated in the vaccine provider's office with diphenhydramine. Because this vaccine contains trace quantities of neomycin, the reaction was also attributed to this excipient (Varivax product circular, 7999909, February 2000).

Study subject 2 (positive for anti-gelatin IgE): On August 15, 1995, a 17-year-old healthy girl developed swelling of lips, wheezing, and trouble swallowing (no hives) 2 minutes after MMR vaccination, diagnosed as anaphylactoid reaction. She was treated with epinephrine and steroids and recovered. The patient reported a history of hay fever, wheezing, and lightheadedness every time she eats chicken or turkey meat, but no symptoms after eating eggs.

Study subject 3 (positive for anti-gelatin IgE): A 12-year-old boy, with mild symptoms of streptococcal pharyngitis, received MMR vaccine on January 8, 1996. Ten minutes after the injection, he developed rhinorrhea and sneezing, followed by tachycardia and hives. The patient was treated with epinephrine, diphenhydramine, and steroids. The reaction resolved in 2 hours.

Study subject 10 (positive for anti-measles IgE): On June 4, 1993, a 15-year-old girl with a history of allergies to pork and lamb meat developed rash on the neck and in the abdomen area, edema and redness of face, itchy throat, and coughing 15 minutes after MMR injection. She fully recovered after treatment with diphenhydramine.

Study subject 13 (positive for anti-gelatin IgE): On January 17, 1992, a 15-month-old healthy boy received a dose of HiB vaccine and then, 5 minutes later, an MMR injection. Immediately after that (within 1 minute), he developed generalized flushing progressing to facial edema and facial and upper body urticaria (no other symptoms). He responded well to epinephrine, diphenhydramine, and dexamethasone. On the next day at home, he had more urticaria treated by the mother with epinephrine, prednisone, and cyproheptadine. The mother observed recurring urticaria throughout most of the child's life, not consistently coinciding with any specific foods. The boy had a history of eating eggs without problems. On an allergy examination, a test for dermographism produced an urticarial reaction. Screening prick tests with common foods were negative. Prick and intradermal tests with MMR vaccine were also negative. The patient was diagnosed with chronic urticaria with dermographism by a consulting allergist.

Study subject 14 (positive for anti-gelatin IgE): A 23-year-old man without a history of allergies received live measles vaccine on March 4, 1994. Approximately 30 minutes after injection, he experienced visual disturbance (pupils dilated to 7 mm), flushing, numbness to the lips, and difficulty swal-

TABLE 2. IgE Testing in Radioimmunoassay: Difference in CPM Values Between 22 Study Subjects and 27 Controls

	Antigen				
	Gelatin	Egg	Measles	Mumps	Rubella
Mean CPM* for cases	0.82	0.57	0.12	0.06	0.03
95% CI	0.67–1.0	0.47–0.71	0.09–0.15	0.05–0.08	0.03–0.04
Mean CPM* for controls	0.57	0.48	0.11	0.07	0.04
95% CI	0.53–0.61	0.43–0.52	0.10–0.13	0.06–0.07	0.03–0.04
Paired t test	$P < .01$	$P = .12$	$P = .37$	$P = .83$	$P = .54$
Random effect model	$P < .01$	$P = .15$	$P = .39$	$P = .84$	$P = .53$

CI indicates confidence interval.
* Expressed as % of total CPM bound to the solid-phase allergen.

TABLE 3. Results of IgE Testing

Case Control Pair	Anti-Gelatin IgE Test (Cutoff = 1.0)		Anti-Egg IgE Test (Cutoff = 1.03)		Anti-Measles IgE Test (Cutoff = 0.33)		Anti-Mumps IgE Test (Cutoff = 0.19)		Anti-Rubella IgE Test (Cutoff = 0.08)	
	% of Total CPM for Cases	% of Total CPM for Controls	% of Total Amount Bound	% of Total Amount Bound	% of Total Amount Bound	% of Total Amount Bound	% of Total Amount Bound	% of Total Amount Bound	% of Total Amount Bound	% of Total Amount Bound
1	**2.05**	0.66	**3.27**	0.68	0.16	0.13	0.11	0.08	0.04	0.04
2	**2.45**	0.42	0.30	0.43	0.06	0.08	0.04	0.04	0.02	0.02
3*	**1.24**	0.58	0.70	0.56	0.14	0.16	0.08	0.08	0.04	0.04
4†§	0.90	0.57	0.45	0.44	0.17	0.11	0.03	0.08	0.03	0.04
5	0.54	0.67	0.33	0.58	0.08	0.07	0.04	0.04	0.02	0.03
6*	0.69	0.64	0.59	0.44	0.11	0.13	0.08	0.08	0.02	0.04
7*	0.56	0.62	0.56	0.48	0.13	0.12	0.08	0.09	0.03	0.04
8	0.85	0.73	0.46	0.47	0.14	0.25	0.09	0.10	0.05	0.05
9	0.85	0.71	0.40	0.48	0.26	0.12	0.04	0.09	0.05	0.04
10	0.60	0.71	0.54	0.63	**0.51**	0.19	0.10	0.08	0.04	0.03
11	0.56	0.51	0.42	0.52	0.10	0.06	0.04	0.03	0.03	0.03
12	0.82	0.71	0.64	0.37	0.11	0.13	0.08	0.08	0.04	0.05
13	**1.01**	0.55	0.64	0.48	0.12	0.12	0.09	0.08	0.03	0.04
14	**1.34**	0.52	0.74	0.52	0.09	0.08	0.06	0.05	0.03	0.03
15	0.82	0.56	0.88	0.95	0.28	0.15	0.12	0.04	0.04	0.02
16	0.53	0.44	0.55	0.42	0.07	0.06	0.05	0.04	0.03	0.03
17	0.62	0.53	0.50	0.34	0.07	0.08	0.06	0.05	0.02	0.02
18	0.50	0.64	0.64	0.45	0.08	0.14	0.08	0.07	0.04	0.05
19	0.43	0.68	0.45	0.78	0.07	0.13	0.04	0.09	0.03	0.03
20	0.62	0.52	0.79	0.39	0.09	0.07	0.05	0.04	0.02	0.03
21	0.69	0.50	0.75	0.46	0.12	0.13	0.09	0.09	0.06	0.04
22	**1.65**	0.49	0.31	0.36	0.07	0.07	0.04	0.04	0.02	0.04

Values in bold represent positive test results. Cases 1 through 12 were classified as probable anaphylaxis; 13 through 22 were classified as possible anaphylaxis (see "Methods").
* Two controls per case.
† Three controls per case.

lowing. He recovered after treatment with epinephrine and diphenhydramine.

Study subject 22 (positive for anti-gelatin IgE): A 5-year-old healthy girl, with a history of hypersensitivity to sulfa, monosodium glutamate, and bee stings, received a dose of MMR vaccine, along with DTaP and OPV on August 7, 1995. In 20 minutes, she developed generalized urticaria and edema. She recovered after treatment with epinephrine and diphenhydramine.

On the basis of the total number of probable and possible cases of anaphylaxis manually reviewed in this study ($n = 168$), as well as the estimated number of doses of MMR, measles, and measles-rubella vaccines distributed in the United States between 1991 and 1997 (approximately 94 000 000), we can calculate a reporting rate of approximately 1.8 cases per 1 000 000 vaccine doses.

Our review of VAERS automated data indicated that there were no substantial increases in the number of selected hypersensitivity reports (coded as anaphylaxis, urticaria or wheezing) during the first 4 years since the introduction of DTaP vaccines for the primary series in the United States in late 1996 to early 1997. Yearly numbers of such reports after MMR (administered alone or in combination with other vaccines, except varicella vaccine) were stable and paralleled MMR vaccine distribution data (Fig 1). A gradual increase in the number of these reports after varicella vaccine (administered alone or simultaneously with other vaccines, including MMR) also parallels a steady varicella vaccine uptake since its licensure in 1995.

DISCUSSION

Six of 22 patients with hypersensitivity to measles-containing vaccination in this study had increased serum anti-gelatin IgE antibody levels. In 1 of these patients, an increased level of anti-egg IgE antibodies was also found. Thus, it is probable that in at least 5 (23%) of the cases, the reaction occurred in response to injection of gelatin in the vaccine. It remains unclear what caused the adverse event in the remaining cases. We did not test for IgE antibodies to neomycin and sorbitol or to latex, which is not an excipient but may, theoretically, get into the vaccine from the rubber stopper of the vaccine vial during reconstitution. Our review of literature indicated that allergic reactions attributed to neomycin or latex in vaccines are extremely rare.[19–22] We did not identify any reports of allergy to sorbitol in vaccines. In this study, we found that a significantly higher proportion of VAERS study subject than controls (28% vs 0%) had a history of food allergies. The practical significance of this observation, however, is not clear. Given a very low risk of anaphylaxis and a relatively high prevalence of food allergies in the general vaccinee population, it would not be feasible to recommend any preimmunization screening.

Findings similar to ours were recently presented by a group of Finnish investigators.[23] In a large, prospective study that examined the reported adverse reactions after the use of almost 3 000 000 doses of MMR II in 1.8 million individuals, they identified 73 presumably allergic reactions, including 30 cases of anaphylaxis. Presence of anti-gelatin IgE antibodies was found in 5 of the 36 individuals (14%), including 2 vaccinees with anaphylaxis when tested in a CAP System radioallergosorbent test. In a more sensitive Immunospot test, 10 (28%) of 36 sera tested had IgE antibodies to gelatin. Significantly more anti-gelatin IgE–positive people (9 of 10) had a history of allergic disorders compared with those who tested negative (9 of 26). In contrast with what has been

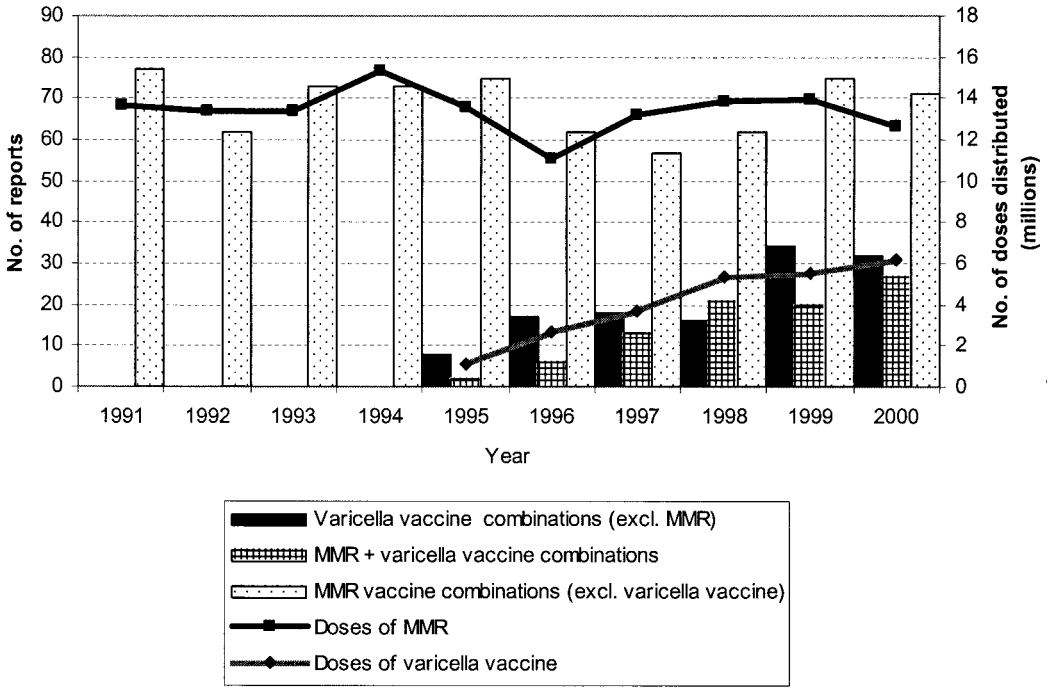

Fig 1. Reporting trends of selected hypersensitivity reactions after MMR and varicella immunization in 0- to 18-year-olds, VAERS, 1991 to 2000 (see explanation in the text).

reported by us and the Finnish investigators, the vast majority of children with immediate-type reaction to measles, mumps, rubella, and varicella single-antigen vaccines in Japan had positive results of IgE tests as measured in the CAP system (86%, 92%, 100%, and 90%, respectively).[24] We believe that this difference is most likely explained by the differences in the type of gelatin used as a part of vaccine stabilizer formulation in live virus vaccines in these countries (Table 4). MMR II gelatin of porcine origin is highly hydrolyzed and has very low molecular weight. In contrast, bovine gelatin added to the single-antigen measles, mumps, and rubella vaccines produced in Japan in the mid-1990s was only partially hydrolyzed and contained a small amount of high molecular weight gelatin. According to Nakayama et al,[25] modifications in the stabilizer formulation for the measles and mumps monovalent vaccines (ie, the 1998 switch in Japan to more hydrolyzed porcine gelatin) may have contributed to a decrease in the incidence of allergic reactions after these vaccines. However, the authors also note that the major reason for this observed decrease is discontinuation of the use of gelatin-containing DTaP vaccines. In the United States, several vaccines that contain gelatin in various quantities were introduced to the national immunization program in the middle of the 1990s (Table 5). In 1995, varicella vaccine (Varivax) was licensed for use in children 12 months to 12 years of age. Since 1997, 2 DTaP vaccines (Acel-Imune and Tripedia) became widely used in the United States for the prime series administered before MMR and varicella immunization. The amount of gelatin in both of these DTaP vaccines (Table 5) is comparable to the amounts of gelatin in 4 of the 6 DTaP products used in Japan (48–200 μg/mL).[11] In light of what was reported from Japan about hypothesized sensitization to gelatin after changes in the Japanese immunization schedule since 1994 and increased reporting of allergic reactions, one would expect to see a similar increase in the United States.[11,26] However, our review of reporting trends of anaphylaxis, urticaria, and wheezing after MMR and varicella vaccination in VAERS does not support this hypothesis (Fig 1). Nonetheless, our cases with anti-gelatin IgE required some previous exposure to gelatin to become sensitized, and this may have come through ingestion of gelatin-containing food or injection of gelatin-containing vaccines.

Genetic differences between the populations studied may provide another explanation for the smaller proportion of IgE-positive cases found in this study. In 1 communication from Japan, it was shown that HLA-DR9, unique to Asians, was typed in 57% of the gelatin IgE–positive patients—a significantly higher proportion than in the control group.[27] In our study, we did not ask about the ethnic origin of study subjects during interviews. However, a review of first and last names of the cases did not suggest Asian origin. Whereas documented allergy to gelatin-containing foods is very rare in the United States (in our study, none of the study subjects or controls reported having food allergy to gelatin), in Japan 7 of 26 children were allergic to gelatin in foods. Difference between foods traditionally preferred in Japanese and Western cultures may also play a role in prevaccine sensitization to gelatin.

Overall the reporting rate of probable and possible anaphylaxis in our study (<2 per 1 000 000 doses of the vaccine distributed) was somewhat lower than estimates from other countries. The highest reporting rate of 10 per 1 000 000 doses of MMR distributed was observed in Finland. A rate of 4.1 cases of anaphylactic and anaphylactoid reactions per 1 000 000 doses of MMR II (Merck) distributed, as reported from Australia after the 1998 Australian measles control campaign, has the same magnitude as the minimum estimated incidence of severe anaphylaxis after measles, mumps, rubella, and varicella single-antigen vaccines in Japan from 1995 to 1997 (6.8, 7.3, 4.4, and 10.3 per 1 million doses of the corresponding vaccine).[24,28] However, comparing these rates is difficult because of the different sensitivities of national surveillance systems for vaccine adverse events.[29]

This study had several limitations. VAERS, like all passive surveillance systems, is subject to underreporting. The reporting rates that we found thus should be considered minimum estimates.[30] In addition, not all potential study subjects could be evaluated because of incomplete data provided with the VAERS report. Because of that, the possibility of misclassification of cases exists. There was a potential for recall bias during collection of allergy history information (ie, the controls could be less likely to

TABLE 4. Differences Between the Type of Gelatin Used as a Component of Stabilizer Formulation in Live Virus Vaccines in Japan and the United States

Vaccine	Animal Source/Origin and Manufacturer	Extent of Hydrolysis	mg Gelatin per 0.5 mL Dose
Measles and mumps monovalent vaccines (Japan) used before 1998	Bovine (Haemaccel, Behringwerke, Frankfurt, Germany)	Hydrolyzed gelatin and, in part, native/intact gelatin	1.5–10 mg*
Measles and mumps monovalent vaccines (Japan) used since September 1998	Porcine modified (Prionex, Pentapharm Ltd, Basel, Switzerland)	Hydrolyzed gelatin only (20 000 Dalton)	1 mg
M-M-R II (Merck) in use since 1979	Porcine (Sol-U-Pro by Dyna-Gel Inc, Calumet, IL)	Highly hydrolyzed gelatin (average size of gelatin peptide fragments = 2000–3000 Dalton)	14.5 mg

* Vaccines by 4 manufacturers used different amounts of gelatin.[7]

TABLE 5. Amounts of Gelatin in US Licensed Vaccines*

Vaccine Type	Vaccine Name (Manufacturer)	Amount (μg) of Gelatin per Dose
DTaP	Acel-Immune (Wyeth, Collegeville, PA)	15
DTaP	Tripedia (Aventis Pasteur, Lyon, France)	28
Influenza	Fluzone (Aventis Pasteur, Lyon, France)	250
Japanese encephalitis	JE-VAX (Aventis Pasteur, Lyon, France)	500
Measles	Attenuvax (Merck, West Point, PA)	14 500
Measles and rubella	MRVAX II (Merck, West Point, PA)	14 500
Measles, mumps, and rubella	MMR II (Merck, West Point, PA)	14 500
Mumps	Mumpsvax (Merck, West Point, PA)	14 500
Mumps and rubella	Biavax II (Merck, West Point, PA)	14 500
Rabies	Rabavert (Chiron Corporation, Emeryville, CA)	12 000
Rubella	Meruvax II (Merck, West Point, PA)	14 500
Varicella	Varivax (Merck, West Point, PA)	12 500
Yellow fever	YF-VAX (Aventis Pasteur, Lyon, France)	7500

* The typhoid vaccine by Vivotif (Berna) contains gelatin in the capsule and is administered orally.

remember past allergic reactions); however, we did not believe that the differences in recall were significant. Because of its retrospective design, the recruitment rate in this study was lower than hoped for (37% of study candidates selected from VAERS were interviewed, of these 39% agreed to be tested). However, we are not aware of reasons that the decision to participate in this study would relate to the levels of anti-gelatin IgE and, as a result, bias our findings.

CONCLUSION

Results from this study support the hypothesis that anaphylaxis after MMR vaccines can in some cases be attributable to hypersensitivity to gelatin. Therefore, we recommend that for patients with a history of severe hypersensitivity reaction to a gelatin-containing vaccine, physicians seek an allergy evaluation (including anti-gelatin IgE testing) before administering a subsequent dose of any gelatin-containing vaccine. Efforts should continue to identify less allergenic substitutes for gelatin currently used by vaccine manufacturers. This study indicates that, in addition to its traditional uses (signal detection, large registry of rare vaccine adverse events), VAERS data can serve as a source of cases for epidemiologic (eg, case-control) studies that evaluate biological factors that might be related to vaccine adverse reactions. Additional studies aiming at identifying other causes of immediate hypersensitivity after immunization with live virus vaccines are warranted.

ACKNOWLEDGMENTS

We thank the following colleagues who assisted us in this study: Lynelle Phillips, RN, MPH (State of Missouri Department of Health, Jefferson City, MO); Paul A. Rota, Alisa Murray, and Janet L. Heath (CDC, Atlanta, GA); and Richard T. Jones, BS, Carol Siegenthaler, RN, Ann M. Harris, RN, and Gregory A. Poland, MD (Mayo Clinic, Rochester, MN).

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